

4.3 An IC/Microfluidic Hybrid Microsystem for 2D Magnetic Manipulation of Individual Biological Cells

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Microfluidics is a powerful technology with promising applications for medical diagnostics and life sciences [1,2]. Microfluidic systems allow manipulation and characterization of biological cells in a biocompatible environment that supports and maintains physiological homeostasis.

In this paper, an IC/Microfluidic hybrid microsystem for 2D magnetic manipulation of individual biological cells is introduced. This system combines the biocompatibility of a microfluidic system with the programmability of an IC. A microfluidic system is fabricated on top of an IC as shown in Fig. 4.3.1. The IC produces spatially patterned magnetic fields utilizing an integrated microelectromagnet array, which is controlled by integrated electronics. The magnetic fields can manipulate individual cells tagged by magnetic beads that are suspended inside the microfluidic system. The spatial patterns of the magnetic fields are dynamically reconfigurable, allowing many different manipulations of individual bead-bound cells, and hence the hybrid system is a *programmable microfluidic system*.

Electric manipulation of biological cells based on dielectrophoresis (DEP) is also feasible with the IC/Microfluidic hybrid system. The DEP-based cell manipulation using an IC chip without a microfluidic system has been reported [3]. In this work, however, the magnetic manipulation scheme is chosen, because the DEP may damage biological cells while magnetic fields are transparent to the cells. In the magnetic method, to impart magnetic moments to biological cells, magnetic beads are attached to target biological cells by coating the beads with specific ligands. While magnetic manipulation of bead-bound cells per se has been widely used, in the conventional method a large group of bead-bound cells are statistically pulled all at once using magnetic fields of low spatial resolution. In the proposed approach the microelectromagnet array produces microscopic magnetic field patterns to move many *individual* cells along different paths.

The microelectromagnet array can be realized in various forms [4]. In this work, integrated microcoils are used as microelectromagnets. Figure 4.3.2 illustrates the implemented microcoil array. For independent magnetic field control, each microcoil is connected to its own on-chip current source. The operating principle of the microcoil array for cell manipulation is to create and move magnetic field peaks by modulating currents in the microcoils. For instance, by activating only one microcoil in the array, a magnetic bead suspended in fluid will be attracted to the field peak at the center of the microcoil on the surface of the IC. Subsequently, by turning off the microcoil while activating an adjacent one, the magnetic field peak is moved to the center of the adjacent microcoil, transporting the magnetic bead to the new peak location. The force on the bead is $F = V\chi/\mu_0\nabla B^2$, where V is the bead volume, χ is the effective magnetic susceptibility of the bead, μ_0 is the magnetic permeability of vacuum, and B is the magnetic field magnitude. The spatial resolution of the manipulation is determined by the spacing between two neighboring coils.

For precise spatial control of individual magnetic beads, the microcoil of Fig. 4.3.2 is carefully designed to generate a single magnetic field peak on the chip surface. The calculated magnetic field profile on the chip surface of the microcoil is shown on the left of Fig. 4.3.3. Note that while the microcoil produces a single magnetic peak on the chip surface, multiple magnetic peaks can exist below the surface as shown on the right of Fig. 4.3.3.

Figure 4.3.4 shows the die micrograph of the prototype IC. This chip integrates an array of 5x5 microcoils whose structure is illustrated in Fig. 4.3.2 and control electronics. This chip, fabricated in a 3M SiGe bipolar technology, occupies an area of 4mm². Microcoils and control electronics are interconnected using mostly bottom metal layers to minimize parasitic magnetic fields.

Figure 4.3.5 shows the photo and the schematic of the IC/Microfluidic hybrid system. The microfluidic system is post-fabricated on top of the chip. Polyimide is spun coated and patterned on top of the chip to form sidewalls of a microfluidic channel, where the channel height and width are 30 and 1000µm, respectively. A glass coverslip, coated with a negative photoresist is sealed on top of the channel sidewalls by curing the photoresist with ultraviolet light. Fluidic tube fittings are separately fabricated and glued to the inlet/outlet of the microfluidic system. To prevent electromigration of the chip and to keep the system temperature at biocompatible 37°C, the hybrid system is mounted on a copper stage cooled by a thermoelectric cooler.

The micrographs in Fig. 4.3.6 show the manipulation of individual magnetic beads using the hybrid system. Magnetic beads of diameter 8.5µm and magnetic susceptibility 0.2 are suspended in distilled water and introduced into the microfluidic channel. Rapid increase of current to 11mA in a microcoil trapped a single magnetic bead at the center of the coil (Image **a**), where the magnitude of the magnetic field peak is 15G and trapping force is 20pN. By turning off the current in the microcoil and simultaneously activating an adjacent coil, the bead is moved to the adjacent coil with an average speed of 1µm/s (Images **b** and **c**). While the magnetic bead is trapped, another magnetic bead is trapped by creating an additional field peak within the coil array (Images **d** to **f**). Repeating the same procedure, multiple beads can be independently yet simultaneously manipulated.

Magnetic manipulation of real biological cells with the hybrid system is demonstrated using bovine capillary endothelial (BCE) cells. Magnetic beads of diameter 250nm and with magnetite content over 90% are incubated with BCE cell culture, leading to the engulfment of 30~50 beads by a BCE cell (Fig. 4.3.7 left). Before performing cell manipulation, the chip surface is treated with bovine serum albumin to suppress binding of the cells to the chip surface. The micrographs in Fig. 4.3.7 show the manipulation of a single BCE cell using the hybrid system. A single magnetic peak (15G) is created, stably trapping a single cell with the trapping force of 50pN (Images **a** and **b**). Subsequently, the trapped cell is moved to adjacent coils with an average speed of 6µm/s (Images **c** to **f**).

The IC/Microfluidic hybrid system allows easy and precise spatial control of individual biological cells with programmable magnetic fields. While the reported IC is in SiGe, it can be fabricated in CMOS technology. The CMOS/Microfluidic hybrid microsystem can be made as a single-use disposable device due to its low fabrication cost. This hybrid system is a tool for performing biological experiments in a standardized, repeatable manner on a microscale.

Acknowledgement:

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- [3] N. Manaresi et al., "A CMOS Chip for Individual Cell Manipulation and Detection," *IEEE J. Solid-State Circuits*, vol. 38, no. 12, pp. 2297-2305, 2003.
- [4] H. Lee, A.M. Purdon, and R.M. Westervelt, "Manipulation of Biological Cells Using a Microelectromagnet Matrix," *Applied Physics Letters*, vol. 85, pp. 1063-1065, 2004.

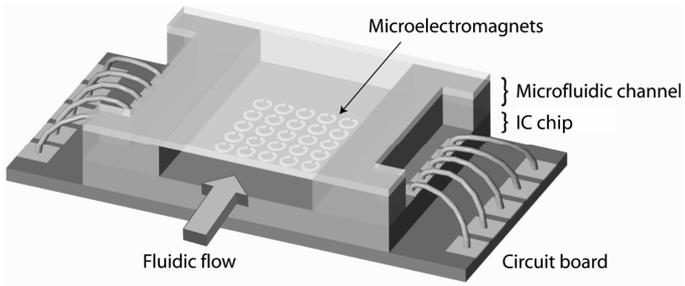


Figure 4.3.1: Schematic of an IC/Microfluidic hybrid microsystem.

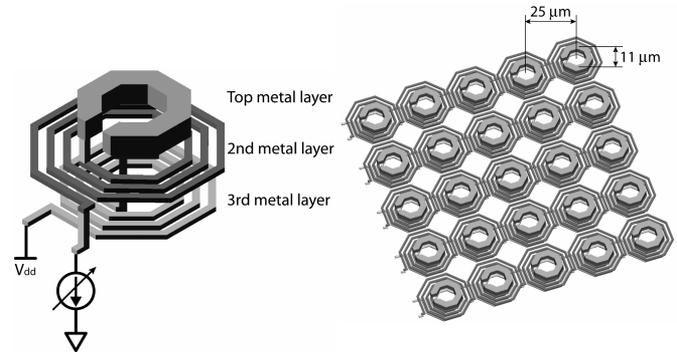


Figure 4.3.2: Schematics of a microcoil array circuit.

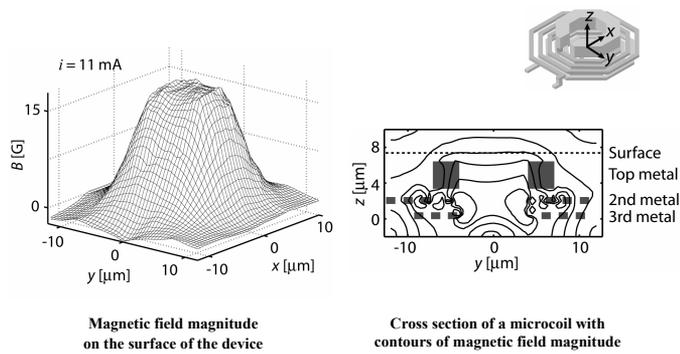
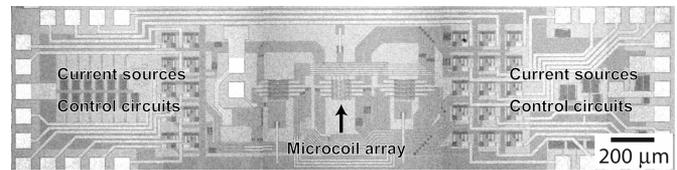
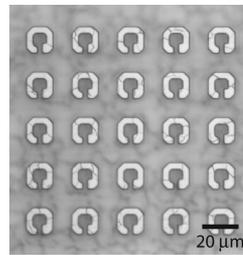


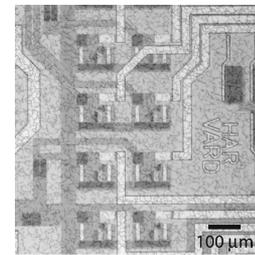
Figure 4.3.3: Magnetic field profiles calculated for a single microcoil.



Chip size 1mm x 4mm



Microcoil array



Control circuits

Figure 4.3.4: Die micrographs of an implemented IC chip.

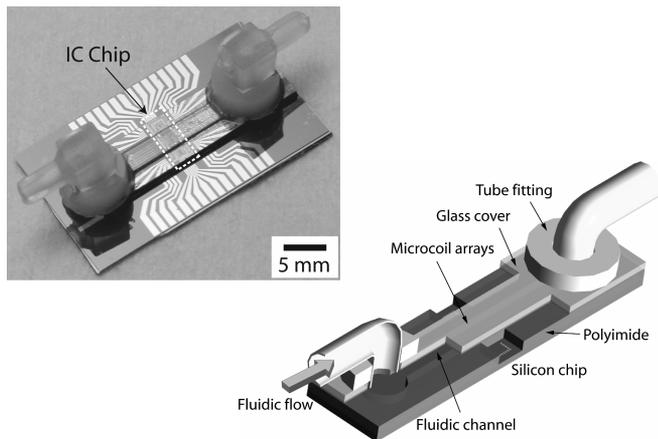


Figure 4.3.5: Photo and schematic of an IC/Microfluidic hybrid microsystem.

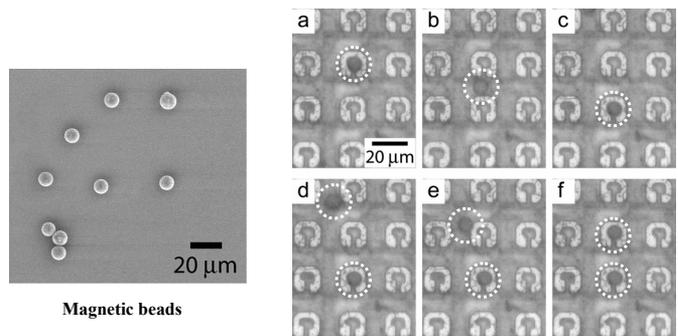
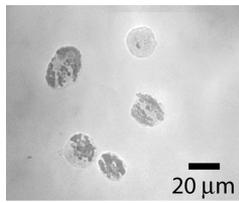


Figure 4.3.6: Manipulation of individual magnetic beads using the IC/Microfluidic hybrid microsystem.

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Bovine capillary endothelial cells with engulfed magnetic beads

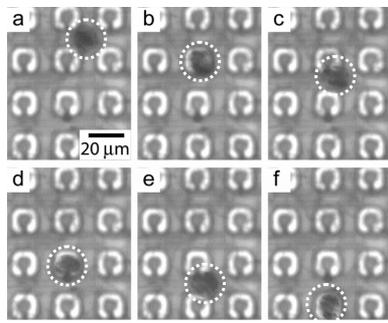


Figure 4.3.7. Manipulation of a single bovine capillary endothelial cell using the IC/Microfluidic hybrid microsystem.